Application no.: 09/943,531 Docket no.: SGL-2020-UT

REMARKS

Claims 7-10 and 13-14 are pending herein after the cancellation of claim 12, entry of claims 13 and 14 and amendment of claim 7. Basis for the amendments and new claims is in the specification throughout (e.g., Example 3 on pages 18-20 and page 2, lines 16-28) and no prohibited new matter has been added.

Applicants acknowledge the withdrawal of the rejection under 35 U.S.C. §102(b). The pending claims are rejected for an alleged lack of enablement. Applicants respectfully traverse this rejection and respectfully request reconsideration in view of the amendments to claim 7 and the remarks hereafter.

The Office rejected claims 7-10 and 12 for alleged lack of enablement under 35 U.S.C. §112, first paragraph. The Office offered four (4) rationale in support of its position that the scope of the previously pending claims allegedly was not enabled by the specification. Each of these rationale are addressed hereafter with respect to the amended claims.

1. Capacity Determinations in Caucasians are Enabled

Claim 7, which was directed to determining the capacity for metabolizing a CYP2C19 substrate in a human, was rejected by the Office for alleged lack of enablement. The Office's main positions were the field allegedly was unpredictable and the frequency of a given marker can vary in different racial populations (e.g., pages 5 and 6 of the action).

Applicants respectfully submit the rejection is inapplicable to the amended claims. Amended claim 7 and its dependent claims are directed to methods for predicting a Caucasian's capacity to metabolize a substrate of a CYP2C19 enzyme. This amendment is introduced for the purpose of expediting prosecution and is in no way an admission that broader populations are not enabled by the specification.

The claimed methods are in accord with the enablement requirements articulated in *In re Wands* and *Ex Parte Foreman*. Specifically, the present specification provides a working example of the claimed methods, in which haplotypes defined by nucleotides at two polymorphic positions in the CYP2C19 5' flanking region were utilized to predict metabolic capacity in a Swedish Caucasian population. Results of the example are summarized in Table 13 on page 20. The specification also provides specific guidance with regard to the population studied, specific

polymorphic positions for haplotype analysis, methodology utilized to determine nucleotides at specific positions for the haplotype analysis, and applying haplotype information for predicting metabolic capacity (e.g., Examples 1, 2 and 3).

If desired, a person of ordinary skill in the art can extend these methods taught in the specification to individuals in other Caucasian populations in a routine manner. The Court of Appeals for the Federal Circuit has deemed a large quantity of experimentation is acceptable when it is routine, (e.g., *In re Wands*, 8 USPQ.2d 1400, 1404 (Fed. Cir. 1988)). These procedures can be carried out in a routine manner given these direct teachings in the specification, especially in view of the high level of skill in the art recognized by the Office (page 9 of the action). Thus, application of the methods taught in the specification to other populations is not undue.

The level of guidance and specific examples in the specification therefore teach application of the claimed methods to Caucasians. A document cited by the Office on page 6 of the action, Ozawa *et al.*, *Drug Metab. Pharmacokin. 19(2)*: 83-95 (2004), provides further evidence that the person of ordinary skill in the art considered studies of Swedish populations as generally indicative of Caucasian population traits. Ozawa *et al.* shows in Figure 1 that omeprazole hydroxylation metabolic profiles from Swedish and Spanish populations are similar, and are distinct from profiles of populations from China and Africa. Ozawa *et al.* also generally group Caucasians together throughout the document and compare the population to Chinese and African populations. Thus, the specific examples in the specification for Swedish populations are representative of Caucasians in general and Applicants are not aware of evidence contrary to this position provided by the Office.

Accordingly, the specification enables metabolic capacity determinations in Caucasians and therefore enables the full scope of claim 7 and its dependent claims.

2. Omeprazole is Representative of Other Substrates

The Office alleges the term "capacity to metabolize a substrate of a CYP2C19 enzyme" is not enabled by the specification as the working examples describe methods for predicting metabolic capacity for one drug, omeprazole, and not multiple drugs. Applicants respectfully submit omeprazole is a model drug that represents CYP2C19 metabolic properties of many other drugs. The specification states on page 3, line 22 that omeprazole is a "marker drug" and documents in the literature refer to the drug as a useful "probe." For example, Caucasians who poorly metabolize omeprazole also poorly metabolize several other drugs, including diazepam, S-mephenytoin and

other anticonvulsants (e.g., hexobarbital) and proguanil, as reported by Andersson *et al., Pharmacogenetics 2*: 25-31 (1992); Balian *et al., Clinical Pharm. Therap. 57(6)*: 662-669 (1995) and Evans *et al., Pharmacogenetics 5*: 64-71 (1995). Chang *et al., Br. J. Clin. Pharmac. 39*: 511-518 (1995) also reported omeprazole better separates extensive from poor metabolizers than mephenytoin (page 515 last paragraph), and therefore is a more advantageous probe. These documents already were cited in an information disclosure statement filed on July 15, 2005 and August 8, 2005.

Accordingly, omeprazole is regarded in the art as a model drug representative of the metabolic properties of other drugs for CYP2C19 assessments. The working examples in the present specification using omeprazole therefore enable the full scope of the claimed methods.

3. Haplotypes of Two or More Positions are Enabled

The Office alleged detecting any two or more polymorphic sites in a CYP2C19 flanking region is not enabled by the specification. Applicants do not understand this assertion and request clarification because the claims are not drawn generally to the detection of two or more polymorphic sites in the CYP2C19 flanking region. Rather, the claimed methods are directed to predicting metabolic capacity based upon a haplotype containing two or more polymorphic sites, where two of the polymorphic sites in the haplotype are specified. These specified sites are at positions 352 and 1060 in SEQ ID NO: 1 of Figure 1, and they alone enable the predictive methods of claim 7 and its dependent claims. These two polymorphic sites define a large portion of the 5' flanking region, and therefore, any other polymorphic sites added to the haplotype would be expected to boost the predictive value.

The specification provides for an additional polymorphic site that can be included in the haplotype at position 269 in SEQ ID NO: 1, and other polymorphic sites could be included in the haplotype. As claim 7 has been amended to specify the polymorphic sites are in the 5' flanking region of the CYP2C19 gene, the region specified in Figure 1 is not so large that additional polymorphisms could be identified and included in the already enabled haplotype analysis. And as noted above, it is expected that additional positions in Figure 1 would enhance the predictive value of the two positions specified in claim 7 since they cover a significant portion of the 5' flanking region. Thus, the full scope of the claimed methods is enabled under these circumstances by the two polymorphic sites in the haplotype defined in independent claim 7.

4. Determining Metabolic Capacity is Enabled

The Office alleged determining any capacity to metabolize a substrate with any nucleotide present or haplotype represented by positions 352 and 1060 is not enabled by the specification. Applicants do not understand this assertion and request clarification.

The Applicants respectfully submit the specification enables the amended claims because metabolic capacities can be predicted from the haplotype claimed without undue experimentation. The specification provides a working example, Example 3, of the claimed methods for determining a metabolic capacity of a CYP2C19 enzyme from a haplotype on each chromosome comprising two or more polymorphic sites in the flanking region of the CYP2C19 gene. Table 13 shows that metabolic ratio can be predicted effectively when a haplotype from each chromosome is determined, and that two polymorphic sites in the haplotype, which are specified in claim 7, are sufficient for making the determination across the range of available metabolic ratios. The polymorphic sites represented in Table 13 are at positions 352 and 1060, which are specified in claim 7, and several haplotype combinations useful for predicting the metabolic ratio are provided. For clarity, the haplotype combinations provided encompass several nucleotide possibilities at each position and on each chromosome. From these haplotype combinations, the specification provides a working example, in Example 3, showing how a metabolic capacity is predicted based upon a haplotype combination. For instance, an individual having a cytosine at each of positions 352 and 1060 on each chromosome is predicted as being a poor metabolizer of a CYP2C19 enzyme substrate.

Thus, several haplotype combinations encompassed by the pending claims are provided in the specification. Other haplotype combinations can be utilized for the claimed methods and the specification provides guidance for their selection. As noted above, the specification provides clear guidance for selecting study populations, specific polymorphic positions for haplotype analysis, methodology utilized to determine nucleotides at specific positions for the haplotype analysis, and applying haplotype information for predicting metabolic capacity (e.g., Examples 1, 2 and 3). If desired, a person of ordinary skill in the art can extend these teachings to other polymorphic sites and haplotype combinations in a routine manner, especially in view of the high level of skill in the art recognized by the Office (page 9 of the action). The Court of Appeals for the Federal Circuit has deemed a large quantity of experimentation is acceptable when it is routine, (e.g., *In re Wands*,

8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). And because the positions already specified in claim 7 (positions 352 and 1060) and disclosed in the specification (position 269) define a large portion of the CYP2C19 5' flanking region, other additional polymorphic sites in the haplotype would be expected to enhance the predictive value of the claimed method. Thus, applying the methods taught in the specification to other polymorphic sites and haplotype combinations is not undue.

Applicants also wish to clarify that claim 7 has been amended to specify the capacity is predicted from the haplotype on each chromosome. Thus, the statement on page 9 of the Office action directed to H2 in Table 13 of the specification is addressed and the combinations of haplotypes in the specification enable the scope of the amended claims.

Thus, the specification provides working examples and specific guidance that enable the claimed methods. As the specification enables the full scope of the amended claims, Applicants respectfully request the Office withdraw its rejection under 35 U.S.C. §112, first paragraph, for alleged lack of enablement.

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CONCLUSIONS

Applicants respectfully submit that the claims pending herein are in condition for allowance, and they earnestly solicit an early notice to such effect. That said, should any issues or questions remain, the Examiner is encouraged to telephone the undersigned at (858) 623-9470 so that they may be promptly resolved.

In the unlikely event the transmittal letter is separated from this document and the Office determines that an extension and/or other relief is required, Applicants petition for any required relief, including extensions of time, and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account 503473.

Respectfully submitted,

Dated: April 10, 2006 By:

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